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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,862	12/10/2003	Katelynne Lyons	LOR-136.0 (9720/88881)	9117

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EXAMINER	
PENG, BO	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
01/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,862	LYONS ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 22, 2007, has been entered.

2. New Claim 47 is added. Accordingly, Claims 1-47 are pending and considered in this Office action.

3. (**Prior rejection-maintained-extended**) The rejection of Claims 1-46 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over (1) Claims 1-78 of 09/930,915; (2) Claims 1-53 of 10/787,734; (3) Claims 98-109 of 10/805,913 and Claims 79-115 of 10/806,006, **is maintained**, now extended to (4) Claims 47-85 of 11/508,655.

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. (**Prior rejection-withdrawn**) The rejection of Claims 1-46 under 35 U.S.C. § 112, first paragraph, for containing new matter, **is withdrawn** in view of the removal of the new matter.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. (**Prior rejection-maintained**) The rejection of Claims 1-6, 8-14, 16-28, 30-42 and 46 under 35 U.S.C. 103(a), as being unpatentable over Pumpens, in view of Zlotnick and Zhang, **is maintained** for the reasons of record.

8. Applicant again argues that the specification Para [0527] shows that C-terminally stabilized C48S/C107S chimer can form particles better than the non-stabilized C48S/C107S control and than C48/C107 HBc. Applicant argues that those results were intuitively unexpected and even more unexpected from the reading of Zheng in conjunction with Zlotnick.

9. Applicant's argument is considered but again found not persuasive. The results shown in the specification are not unexpected because they are consistent with the teachings of Zlonick and Zheng.

10. Zlotnick teaches that C-terminal Cys can stabilize HBcΔ. Zlotnick shows that the Cp*150 capsid, which is Cys C-terminally stabilized HBcΔ, is more stable than Cp*149, which is HBcΔ without the C-terminal Cys. Zlonick used SDS/PAGE gel and size exclusion chromatograph analyses (see Figure 2a and 2b, right column 9557) to teach that Cp*150 forms disulfide dimers at pH 7.5 and 9, but Cys-free Cp*149 does not. Zlotnick has also shown that the Cp*150 capsid is resistant to dissociation by 3.5 M urea, suggesting that disulfide bond formation by Cp*150

can promote capsid assembly (Results and Discussion, paragraph 1 and 2, p. 9558). Using cryo-electron microscopy, Zlotnick shows that Cp*150 capsid has well defined densities (right col. p.9559-p.9559, and Figure 4d-f). As a result, Zlotnick clearly teaches that HBcΔ with C-terminal Cys is more stable than HBcΔ without C-terminal Cys.

11. Regarding the roles of native Cys48, Cys61 and Cys183 in forming HBc dimers, Zhang teaches that Cys 61 is always involved and Cys48 is partially involved in interchain disulfide bonds with the identical monomer, whereas Cys183(C-termini) is always involved in a disulfide bond with the Cys183 of another monomer (Abstract). Zhang shows that a single mutation at Cys48 produced only dimers with no detectable monomers (Figure 3, lane 3), and mutations at both Cys48 and Cys107 results in only dimers (Para 3, right col. and also see Figure 3, lane 7). By shwing these results, thus, Zhang teaches that Cys48 and Cys107 are not essential for formation of an interchain disulfide bond with another monomer because mutations of Cys48 and Cys107 do not affect formation of HBc dimers. Moreover, these results also illustrate that mutation(s) of Cys48 and/or Cys107 results in only HBc dimers, rather than a mixture of dimers and monomers (Para 2, right col. p. 9424, and Figure 3), which would have suggested to and motivated one of ordinary skill in the art to change native Cys48 and Cys107 in order to obtain unified HBc dimers.

12. Given the knowledge that Cys48 and Cys107 are not essential for native core particle formation as taught by Zhang, given the knowledge that mutations of Cys48 and Cys107 result in only HBc dimers as taught by Zhang, and also given the knowledge that HBcΔ with C-terminal Cys is more stable than HBcΔ without C-terminal Cys, one of ordinary skill in the art is capable to correctly apply such knowledge to the design of an HBcΔ chimer, and would have created the

alleged HBcΔ chimer containing Cys at its C-termini and substituted amino acids at Cys48 and Cys107. In view of the teachings of Zlotnick and Zhang, one of ordinary skill in the art would recognize that Applicant's results, showing that C-terminally stabilized C48S/C107S chimer can form particles better than the non-stabilized C48S/C107S control and C48/C107 HBc, are expected because they are consistent with teachings of Zlotnick and Zhang.

13. **(Prior rejection-maintained)** The rejection of Claims 1-6, 8-28, and 30-46 under 35 U.S.C. 103(a), as being unpatentable over Page and Birkett, both in view of Zhang, **is maintained** for the reasons of record.

14. Applicant argues that because Zhang teaches that Cys48 is partially involved in the interchain disulfide bonding, the alleged C48S/C107S HBc chimer lacking Cys48 shows greater stability than the otherwise identical chimer possessing a Cys48 residue (See [0527]). They claim that this finding is unexpected and patentable.

15. Applicant's argument is not convincing. As discussed above (Para 10-12), the claimed result is not unexpected because the cited references have provided specific teaching about the roles of Cys48, Cys107 and C-terminal Cys in forming HBcΔ particles. It is within the knowledge of one of ordinary skill in the art to correctly apply such knowledge to the molecule design in order to achieve more stabilized HBcΔ particles. Therefore, the invention as a whole is obvious to one of ordinary skill in art in view of the prior art.

16. Following is new rejection necessitated by the amendment:

Claim Rejections – 35 USC § 112-Scope of enablement

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. **(Restated rejection necessitated by the amendment.** Also see Office action dated 12/17/04) Claims 1-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a HBc chimer of SEQ ID NO: 1, does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

19. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors that are considered most relevant are the presence or absence of working examples, the direction or guidance presented, and the nature of the invention.

20. Claims 1, 11, 25 and 47 specify a chimer molecule with up to about 5 percent substituted amino acid residues in the HBc sequence. The scope of claims encompasses a large number of HBc chimers that contain 5% substitutions variously arranged along the sequence of SEQ ID No: 1. As a result, Claims 1, 11, 25 and 47 encompass a large number of alleged HBc chimers with no defined structure. Although Applicant has disclosed that one species HBcΔ is used to construct HBc chimers in the specification, Applicant has not disclosed sufficient species of alternative HBc variants for HBc chimers. More importantly, the specification has not shown that such alleged HBc chimers containing 5% substitutions can still form viral-like particles like HBc. Applicant fails to provide the necessary guidance that would lead one to such molecules. First note, it is stated as substituted and not conservatively substituted. Therefore, it seems more than reasonable to assume that a nonconservative substitution in the amino acid sequence will have a deleterious effect on the conformation of the HBc molecule. Second, even a single substitution can have an unpredictable effect on conformation of the resulting molecule. "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." See Rudinger, J. at page 6 (Cited in the previous Office action dated). Thus, a single amino acid can create problems resulting from changes in conformation that can't be adequately predicted in advance.

21. Thus, based on the disclosure in the application, and on the knowledge in the art, those skill in the art would not be able to make alleged stabilized HBc chimers containing 5% substituted amino acid residues in the HBc SEQ ID NO: 1

Remarks

22. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
January 7, 2008